

# CENTER FOR COMPARATIVE MEDICINE

Tools to support Research and  
development with experience and quality



ICIVET LITORAL



UNL • FACULTAD  
DE CIENCIAS  
VETERINARIAS

## ABOUT THE CENTER FOR COMPARATIVE MEDICINE

1997-2020, over 20 years providing high complexity technological support for biomedical research

### MISSION

To support institutions and companies that require laboratory animals of high genetic and sanitary quality and/or the performance of high complexity bioassays following international ethics and welfare standards.

### VISION

To constitute a center of national reference for the performance of complex bioassays that allow generation of knowledge in order to improve health and welfare of humans and animals.

### VALUES

- Ethic in the use and care of animals through the respect of ethics and welfare standards.
- Ethic and commitment to the job.
- Commitment to society and environment.
- Quality and professionalism in performance of all activities.
- Team work.

The general objective of the Center for Comparative Medicine (CMC), at the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral (Esperanza, Santa Fe, Argentina), is to do research with laboratory animals following international standards of ethics and quality regarding their use and care.

The CMC was established in August 1997 by teachers and researchers interested in the care and use of laboratory animals, primarily for research in veterinary science, medicine and biology. The CMC currently boasts with a total area of approximately 700 m<sup>2</sup>, including areas for production of different laboratory animals, biological testing, quality management and administrative offices. In addition, there are 450 m<sup>2</sup> of high complexity laboratories associated with the Center. Since March 2013, the CMC has become part of the Instituto de Ciencias Veterinarias del Litoral (Institute of Veterinary Sciences of Litoral; ICiVet-Litoral), an Institute that belongs to the Scientific and Technical Research Council of Argentina (CONICET) and Universidad Nacional del Litoral. Since 2016 to date, the CMC is the first and only center integrated to an institution of the Scientific and Technological System in the country that combines the certifications and qualifications corresponding to SENASA, ANMAT, ISO 9001 and GLP-OECD. The CMC has been a member of the National Bioterrial System (NBS) of the Ministry of Science, Technology and Productive Innovation since 2014.

In 2019, the CMC received the National Quality Award by the National Direction of Processes, Quality and Efficiency of Management from the Government Secretary of Modernization.

Activities at the CMC are focused on improving animal and human health, through the provision of laboratory animals and the development of experimental models and high complexity biological assays required for improving products and biomedical procedures.

The team includes Veterinarians, Biologists, Biochemists, and graduates in Biodiversity and Biotechnology, as well as technicians specialized in the care of laboratory animals. The team thus covers different areas of the biomedical sciences such as pathology, microbiology, parasitology, pharmacology, toxicology, cell culture, immunology, imaging, fine chemistry, biochemistry, ethics and molecular biology, among others.

Laboratory animals are for medical science researchers, what a drawing panel is for an architect, or a chemical reagent for a chemist. Moreover, laboratory animals of high quality are required for pharmacological and toxicological tests as well as for everything related to microbiology and physiology. More importantly, it is essential to respect national and international standards on Ethics in Experimentation and Animal Welfare while using them. The work carried out at the CMC complies with the principles of international guidelines for research involving laboratory animals.



## QUALITY MANAGEMENT

All records of the quality management system are available for on-site audit.



The CMC has implemented a Quality Management System certified according to the IRAM-ISO 9001 standards and declared by the Argentine Accreditation Organization (OAA) to be in accordance with the requirements for Good Laboratory Practices (GLP) of the Organization for Economic Co-operation and Development (OECD) to conduct non-clinical studies. In particular, some areas of competence are toxicity and mutagenicity assays of pharmaceutical products, industrial chemical reagents and agrochemicals, and toxicokinetic and pharmacokinetic assays of pharmaceutical products.

The Quality Management System, which is the result of the quality policy defined by the Board of Directors of the CMC, includes the organizational structure, functions, activities, resources, staff training and necessary documentation to ensure that the services provided meet the expectations of customers in addition to legal and regulatory requirements related to the activity.

The functioning of the organization following a Quality Management System provides control and forecast when providing laboratory animals and carrying out services entrusted by third parties, thus lowering risks of disruptions during their performance and thus leading to an increase in the productivity of the organization and in the fidelity of our customers. In addition, the CMC has very strict and specific procedures to ensure the confidentiality of the relationship with customers.

The CMC also has a quality measurement and monitoring system that allows the continuous improvement of procedures to detect and thoroughly analyze possible problematic aspects and thus implement the necessary actions to correct the causes of problems, in order to prevent them from reappearing. The organizational process includes periodic internal audits to each of the areas that encompass the CMC. In addition, clients and certification authorities make permanent audits to different processes within the CMC, actions that have led to many improvements in these processes.

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### The Quality Management System of the CMC is reflected on the following documents:

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Quality manual

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Standard operative procedures (SOPs)

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Instructional charts

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Analytical techniques

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Organization charts

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Records

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## ACKNOWLEDGEMENTS, ACCREDITATIONS AND CERTIFICATIONS



Premio Nacional a la Calidad



Cámara de Senadores  
de la Provincia  
de Santa Fe



GESTIÓN  
DE LA CALIDAD

IR-9000-0006005

Producción de ratas, ratones y conejos de laboratorio de cepas reconocidas y el diseño, ejecución y control de ensayos biológicos destinados a instituciones científicas, académicas y empresas.



SERVICIO NACIONAL DE SANIDAD  
Y CALIDAD AGROALIMENTARIA



BPL-OCDE

Cumplimiento de Buenas  
Prácticas de Laboratorio



Sistemas Nacionales  
Bioterios

### ANMAT

In 2007, the CMC adopted compliance of «Good laboratory practices» (GLP), which has been verified by the National Institute of Medicines (INAME) of the National Administration of Drugs, Food and Medical Technology (ANMAT, Argentina), certifying compliance with ANMAT decree 6344/96, which refers to the «Regulation for Bioterium from laboratories that elaborate medicinal specialties and/or perform analysis for third parties».

### IRAM - ISO 9001:2015

In 2014, the CMC has certified its Quality Management System according to the IRAM-ISO 9001 standard, under the registration number 9000-0006005, whose scope is «Production of rats, mice and rabbits of accepted strains, and design, performance and control of bioassays, commissioned by academic and scientific institutions and private companies».

### NATIONAL SYSTEM FOR ANIMAL FACILITIES CENTERS

Since 2014, the CMC has been a member (ID 841) of the National System for Animal Facilities Centers (SNB) of the Ministry of Science, Technology and Productive Innovation.

### NATIONAL QUALITY AWARD

In 2019, the CMC received the National Quality Award by the National Direction of Processes, Quality and Efficiency of Management, of the Government Secretary of Modernization.

### SENASA

Since 2008, the CMC is part of the National Network of Assay and Diagnosis Laboratories, from the National Service of Animal Sanitation and Food Quality (N° LR0139, SENASA, Argentina), which authorizes the supply of laboratory animals and performance of bioassays, according to Resolution N° 736/06. In addition, the CMC has certified to be in compliance with Resolution N° 617/2002, which refers to «Requirements, conditions and procedures for the technical qualification of laboratories holding animal production, maintenance and experimentation facilities».

### GOOD LABORATORY PRACTICES (GLP)

The CMC has been declared by the Argentine Accreditation Organization (OAA) to be in accordance with Good Laboratory Practices (GLP-OECD) for conducting preclinical studies. In particular, the areas of expertise include toxicity, mutagenicity, toxicokinetic, pharmacokinetic and preclinical safety assessments of biotech, pharmaceutical, chemical and agrochemical products. Conformity Record with GLP-018E.

### ACKNOWLEDGEMENT BY THE SANTA FE PROVINCE SENATE CHAMBER

In 2019, the Senate Chamber of Santa Fe acknowledged the CMC for its contributions in health improvement through the development of experimental models and highly complex bioassays, which are required for the improvement of pharmaceutical products and biomedical procedures.

## OUR OBJECTIVE

The overall goal of the CMC is to provide an integrated approach to research with laboratory animals and alternative methods, following strict quality standards.

### OVERALL AIMS

- To produce high quality laboratory animals in sufficient numbers. To design and execute biomedical assays, ensuring high quality, to meet the requirements of different costumers.
- To ensure respect for national and international standards on the care and use of animals for experimentation and other scientific purposes.

### SPECIFIC AIMS

- To encourage the development of basic and applied research on the use of animal models.
- To contribute to the generation of knowledge in order to improve health and welfare of humans and animals.
- To provide excellence technological support services.
- To constitute a regional reference center and spread knowledge that highlights the importance of the use of experimental models in the study of biomedical sciences.
- To contribute to the integral formation of professionals in Veterinary Sciences.
- To provide infrastructure and support for research and training of human resources within the scope of the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral and researchers from other public and private institutions that require it.



## ETHICS AND WELFARE

The use of animals in research, teaching, and biological testing, is only acceptable if it effectively contributes to a better understanding of biological principles and if it can not be replaced with alternative methods.

Animal experimentation is one of the fundamental pieces in biomedicine, regarding research projects, diagnostic tests and controls for pharmacological products. On its 11th Inter-American Meeting of 1980, the Pan American Health Organization (PAHO) expressed that: «countries which have achieved a breakthrough in the control of human and animal diseases are those that have established entities dedicated to a better development of the Science of Laboratory Animals».

The use of animals in research, teaching, and biological testing, is only acceptable if it effectively contributes to a better understanding of biological principles and if it can not be replaced with alternative methods.

Animals should be used only when the researcher has already unsuccessfully sought for an acceptable alternative. The continuous exchange of knowledge, literature review, and adherence to the principles of «Three Rs» of Russell-Burch (Replacement, Reduction, and Refinement) are other necessary conditions. Researchers who use animals should use the most humanitarian methods available, make that the number used is the smallest possible, and use the appropriate species for valid results.

The work carried out at the CMC comply with the principles of international guidelines for use and care of laboratory animals, as well as ethical guidelines for bioassays.

In addition, the FCV has an Advisory Committee of Ethics and Safety (CAES), which was created to ensure that the activities that involve the use of animals, carried out at the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral, are conducted humanely and following international standards of ethics and biosafety. All protocols and standard operating procedures held at the CMC are assessed and approved by this Committee.





## FACILITIES OF THE CMC

There is an area of productive biological trials with cages and facilities for the management of large animals during clinical assays.

The CMC has 700 m<sup>2</sup> of covered space, integrating those areas destined to the production of different animal species, biological testing, quality management and several outbuildings for administration, maintenance and storage rooms. All the rooms, including those for both production and biological testing, have automated controls of temperature, illumination and air renewal with high efficiency filtering systems.

The production area has four rooms for breeding and stock, as well as changing rooms, laundries, preparation of materials and an independent storage room.

The area of biological testing has rooms for the maintenance of different species, boxes for the housing of large animals, a separate room for isolation and quarantine, and laboratories for general procedures and initial processing of samples.

There is also an administrative area, with a meeting room with a video conference system, an archive room with a system of fire protection, and research and development offices.

The facilities have a security system that allows the permanent remote monitoring of all the areas of the CMC by using high resolution cameras, as well as the equipment and environments control through specific sensors placed on each of them that ensure immediate response in case of any kind of emergency.

The building is integrated into the Faculty of Veterinary Sciences of the Universidad Nacional del Litoral and the ICIVET-Litoral (UNL-CONICET), in direct relation to its highly complex laboratories. This allows a comprehensive approach to complex experimental protocols.




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### These fully installed laboratories include:

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Area of *in vitro* assay

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Laboratory of applied cellular and molecular biology

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Laboratory of clinical trials

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Laboratory of pharmacology and toxicology

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Laboratory of food analysis

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Laboratory of image analysis

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Laboratory of microbiology

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Laboratory of parasitology

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Laboratory of histology and pathological anatomy

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Radiology and diagnostic imaging facilities

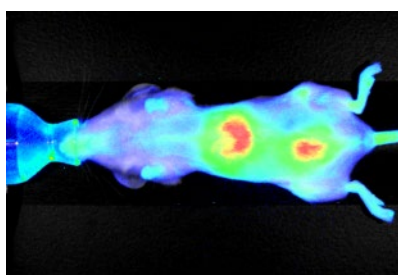
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Operating room of high complexity

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## EQUIPMENT

### GENERAL



Air conditioning system with high efficiency filtering.
Individually ventilated cages (IVC systems).
Animal transfer stations with protection class II.
Biological safety hoods.
Emergency power system.
Autoclave sterilizer.
Automatic monitoring of environmental conditions system.
Digital portable ultrasound scanner, model Chison 8300 vet.
Emptying system of beds with high security.
Ultrafreezers.
High performance computer servers.
Integral system for building safety.
Automatic infusion pumps and anesthesia monitoring system.
Pearl Trilogy Bioluminescence and IR Fluorescence Imaging System.
Color Doppler Ultrasound (Mindray Z6Vet).
IVIS SpectrumCT PerkinElmer Bioimaging System.

### ANALYTICAL EQUIPMENT



Cellular and molecular biology equipment (real time thermocyclers, digital microscopes, etc.) for diagnosis and health monitoring.
Near infrared (NIR) spectrophotometer, Shimadzu Prestige.
Clinical chemistry autoanalyzer, Metrolab 2300 plus.
Hematology autoanalyzer, Mindray BC-2800Vet.
Cellular and tissue culture laboratory fully equipped for in vitro assays.
Acoustic Focusing Flow Cytometer, Attune NxT.
Full UV/visible spectrum microplate readers, SPECTROStar Nano and CLARIOStar BMG LABTECH.



### R FLUORESCENCE AND BIOLUMINESCENCE IMAGING SYSTEM PEARL TRILOGY

An image capturing system for small animals allows the precise detection of small and deep targets.

Its direct applications include: receptor marking, biodistribution assays, vascular and lymphatic network visualization, structural imaging and bioluminescence.

### MASS SPECTROMETRY

A LC-MS/MS system, consisting of a Shimadzu UFLC XR liquid chromatograph and a triple quadrupole mass spectrometer with linear ion trap AB Sciex Q-Trap 3200, allows the identification and quantification of molecules within different matrices with very high specificity and sensitivity.







### FLOW CYTOMETRY

An acoustic focusing flow cytometer ATTUNE NXT allows detecting the presence of molecules and materials of interest by immunofluorescence techniques, fluorescent sensors or fusion to fluorescent proteins, both in fixed particles and in living cells, which makes it possible to address, among others, the study of cellular dynamic processes and identifying cell populations in specific models.

### HISTOPATHOLOGICAL STUDIES

A histopathology laboratory, which integrates veterinary pathologists with extensive training in the area, along with the advanced technology that includes microtomes and automatic microscopes equipped with digital imaging systems and a panel of more than 300 antibodies, enables the efficient resolution of findings through immunohistochemical techniques.

### COLOR DOPPLER ULTRASOUND SCANNER

A doppler ultrasound scanner Mindray Z6Vet, with high frequency linear and microconvex transducers, allows obtaining high resolution images that facilitate correct data collection in different studies. It is useful in the exploration of organs and structures in lab animals, including abdominal, small parts, cardiovascular and ophthalmological studies. In addition, since it has a doppler ultrasound system, it allows to evaluate the speed, direction and spectral frequency, as well as the indices of resistance and pulsatility, of the blood flow. These benefits are essential

during the assessment of tumor development and response to treatments in *in vivo* models applied to oncology, among many other benefits.

### HEMATOLOGY AUTOANALYZER

An automatic analyzer Mindray BC-2800 Vet allows to perform all the analytical stages of hematology following GLP and being monitored by the Quality Management Area of the CMC. This equipment has validated routines for different species and allows the automatic and small volume analysis of 19 hematological biomarkers in different toxicology and safety tests.

### DIGITAL ELECTROCARDIOGRAPH

A Cardiacom Digital CC12Der device allows to respond to international standards that require the evaluation of cardiotoxicity in preclinical trials of new medicines intended for use in humans. It works with seven simultaneous leads, manual and automatic scanning, and a specific software for laboratory animals that automates the analysis of the different segments of the electrocardiogram.

### IVIS SPECTRUM CT

High performance bioimaging system, 2D bioluminescence, multi-wavelength 2D fluorescence imaging, transillumination fluorescence, X-ray and 3D tomography.

## ANIMALS

The CMC has its own production of genetically certified mice, rats and rabbits and has registered its own international laboratory code (Cmedc) at the Institute for Laboratory Animal Research (The National Academies of Sciences, Engineering, and Medicine, USA). In addition, it has areas available for the maintenance of other species often used in biological trials such as poultry, pigs and cattle, and it is considered to add a specific area to develop models of immunosuppressed animals

### 1. RATS

Wistar/Cmedc strain: Strain of own production, currently stabilized with inbreeding superior to F30.

### 2. MICE

BALB/c Cmedc strain: Strain derived from animals of the Jackson Laboratory (USA), currently with inbreeding superior to F20.

C57BL/6: Strain a strain derived from animals of the Jackson Laboratory (USA).

### 3. RABBITS

New Zealand Breed: Animals produced in our Center, coming from colonies acquired in the best ranches of the country, with genetic certification granted by the Sociedad Rural Argentina.



# CMC

ONLY CENTER INTEGRATED TO AN INSTITUTION OF THE  
SCIENTIFIC - TECHNOLOGICAL SYSTEM IN THE COUNTRY  
THAT CONJUGATES THE CERTIFICATIONS AND APPROVALS  
CORRESPONDING TO SENASA, ANMAT, ISO 9001  
AND GOOD LABORATORY PRACTICES (GLP-OECD).

NATIONAL QUALITY AWARD 2019.



## SERVICES AND OFFERS

### High complexity biological trials following strict quality management systems

The main services provided include production and sale of animals, and the performance of tests with different complexity, including among others: the production of hyperimmune sera, specific protocols and research projects, complex multidisciplinary trials, surgeries, immunogenicity studies, *in vitro* tests, comprehensive preclinical evaluation of biopharmaceuticals, counseling on regulatory aspects.

The CMC also seeks to provide users with a place to carry out all the work within the facilities, assigning specific rooms to each test and thus avoiding the need to move the animals to areas that do not meet the corresponding standards or their manipulation by unqualified staff.

In recent years, the CMC has provided services to more than 60 research and development groups related to National Universities and Institutes from CONICET, and to more than 50 companies from the pharmaceutical and health sectors. These users come from different parts of the country and abroad, and have the necessary logistics for the transport of animals and samples.



Provision of animals for the development of research and teaching activities.

Advising for the installation of Animal Facilities Centers and Test Areas.

Design and execution of biological trials according to national and international standards (SENASA, ANMAT, OPPT, OECD, FDA, EMA, EPA, ICH, Pharmacopoeias, etc.).

Planning and development of preclinical trials of high complexity according to national and international standards (ANMAT, FDA, EMA, ICH, ANVISA).

Planning and development of field clinical trials in farm animals, according to national and international standards (SENASA, VICH).

Biological evaluation of medical devices according to the ISO 10993 standard.

Development of specific experimental models of high complexity.

Quality control and biological activity control of drugs according to pharmacopoeias.

Safety tests.

Pyrogen test.

Acute, subacute and chronic toxicity tests.

Biocompatibility studies.

Tolerance and sensitization tests.

Studies of carcinogenesis, reproductive toxicology and teratogenicity.

Pharmacokinetic and toxicokinetic studies.

*In vitro* assays.

Preparation of polyclonal sera.

Molecular biology techniques.

Biochemical studies.

Pharmacological studies.

Toxicological studies.

Histopathological studies.

Immunologic studies.

Experimental surgeries.

Regulatory studies

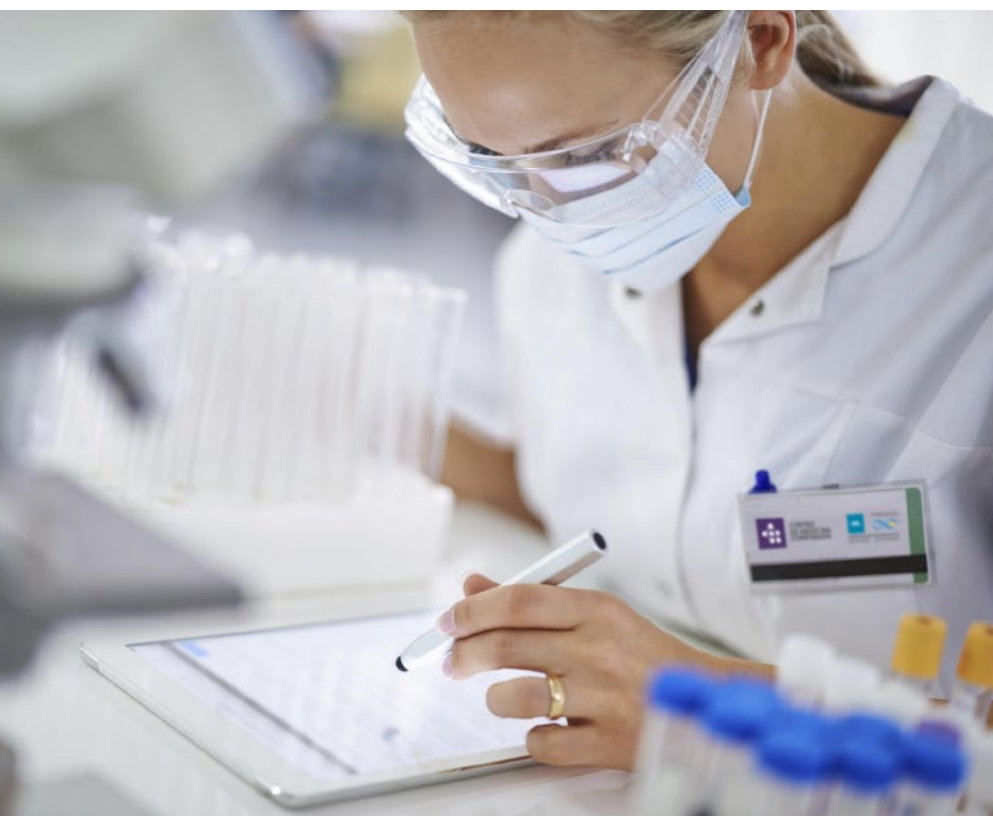
Development of analytical methods

Residues and time of withdrawal studies for veterinary drugs

The CMC has a Quality Management System certified by ISO 9001 for the provision of animals, and the tests are performed in accordance with Good Laboratory Practices (GLP-OECD). This system includes the organizational structure, functions, activities, resources and documentation necessary to ensure that the services provided meet customers' expectations in addition to regulatory and legal requirements related to the activity. All records are available for on-site auditing.

## MONITORING AND QUALITY CONTROL

Periodically, the microbiological monitoring of: supplies (bed, food and water), animals from the production and stock colonies, is performed in order to evaluate different health aspects. It is also performed the chemical monitoring of bed, food and water to test for agrochemicals. In addition, microbiological and genetic monitoring is carried out in external laboratories of worldwide reference, in order to evaluate the presence of frequent pathogens in laboratory animals and the genetic quality of our animals. The controls performed include the specific pathogens and parasites listed in the corresponding reports that are recognized for causing disease or compromising health status. Opportunistic agents are also detected, however, some of them are tolerated on the basis of international guidelines. The production data of all species are under a system of good practices, with archived records that allow the traceability of all the animals used or sold.



## RESEARCH AND TRANSFER

Research and transfer projects are carried out within the CMC, and they have allowed for the constant growth of the Center's operational capacities and the generation of knowledge in the field of comparative medicine. Several of these projects have been carried out in collaboration with companies from the pharmaceutical sector of the country and abroad.

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**25**

Years of experience  
in applied research

**+2000**

Protocols performed

**23000**

Animals produced annually

**700 M<sup>2</sup>**

dedicated exclusively

**450 M<sup>2</sup>**

of support laboratories

**80**

Professionals in our  
work team

**20**

R&D agreements

**25**

Technological services  
in progress

**3**

Public-private projects  
carried out

**+25**

Technological development  
projects in progress

**+60**

Research groups use our  
services and advice

**+50**

Companies use our  
services and advice



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